JACC Vol. 3, No. 3
March 1984:857-64

Clinical Efficacy and Electrophysiologic Effects of Cibenzoline Therapy in Patients With Ventricular Arrhythmias

KEVIN F. BROWNE, MD, ERIC N. PRYSTOWSKY, MD, FACC, DOUGLAS P. ZIPES, MD, FACC, DONALD A. CHILSON, MD, JAMES J. HEGER, MD, FACC

Indianapolis, Indiana

Cibenzoline, a new antiarrhythmic agent, was tested in 26 patients who had symptomatic ventricular tachycardia (24 patients) or premature ventricular complexes (2 patients) unresponsive to conventional drugs. Cibenzoline was given orally every 8 hours to maximal doses of 65 mg in 2 patients, 81.25 mg in 22 patients and 97.5 mg in 2 patients. Cibenzoline abolished spontaneous episodes of ventricular tachycardia in 8 of 16 patients with ventricular tachycardia during a 72 hour control electrocardiographic recording, and 7 of 22 patients had greater than 83% decrease in premature ventricular complexes compared with control. The PR interval increased 14% ($p < 0.001$), QRS duration increased 17% ($p < 0.001$), QT interval did not change and mean ejection fraction in 10 patients did not change.

Electrophysiologic studies were performed on 10 patients in the control period and during maximal cibenzoline dosage. Cibenzoline did not affect electrophysiologic properties of the atrium or atrioventricular (AV) node. It prolonged the ventricular effective (223 ± 16 to 241 ± 22 ms, $p < 0.02$) and functional (247 ± 18 to 264 ± 25 ms, $p < 0.02$) refractory periods. At control electrophysiologic studies, ventricular tachycardia was induced in 9 of 10 patients (mean cycle length 210 ± 31 ms). Cibenzoline therapy prevented ventricular tachycardia induction in two patients, and in the other seven patients the mean ventricular tachycardia cycle length increased from 210 to 260 ms. The one patient with no ventricular arrhythmia induced during the control study still had no arrhythmia induced while receiving cibenzoline. Among six patients receiving cibenzoline during follow-up, one patient died of recurrent myocardial infarction, two patients stopped taking cibenzoline because of recurrent ventricular tachycardia and three patients have continued taking cibenzoline for 10 ± 4 months with control of symptomatic arrhythmias.

Thus, cibenzoline suppressed ventricular tachycardia and premature ventricular complexes in some patients unresponsive to conventional drugs and was well tolerated. Cibenzoline significantly prolonged ventricular effective and functional refractory periods and had minimal negative hemodynamic effects.

Cibenzoline is an imidazoline derivative (4,5-dihydro-2[2,2-diphenyl-cyclopropyl]-1H-imidazole butanedioate [1:1]) salt (Fig. 1) that is currently undergoing clinical investigation in the United States as an antiarrhythmic agent. In isolated rabbit atria, cibenzoline decreased action potential amplitude, maximal rate of depolarization and conduction velocity and prolonged action potential duration (1). In intact dogs, cibenzoline produced a slight decrease in myocardial contractility with no effect on blood pressure or myocardial blood flow (2).

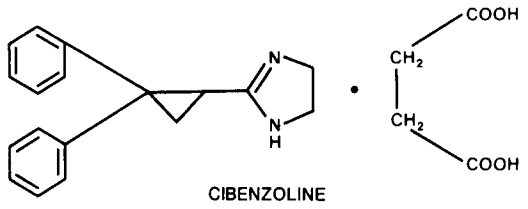
Clinical studies in Europe (2) showed that oral cibenzoline was as effective as disopyramide and more effective than nadoxolol, a beta-adrenergic blocking agent, in suppressing premature ventricular complexes in patients with chronic arrhythmias, and intravenous cibenzoline was as effective as intravenous lidocaine in suppression of chronic premature ventricular complexes but was noted to decrease left ventricular function more than lidocaine. The purpose of this study was to investigate the antiarrhythmic, hemodynamic and electrophysiologic effects of cibenzoline in patients who have symptomatic ventricular arrhythmias unresponsive to conventional antiarrhythmic drugs.

From the Krannert Institute of Cardiology, the Department of Medicine, Indiana University School of Medicine, and from the Veterans Administration Medical Center, Indianapolis, Indiana. This study was supported in part by the Herman C. Krannert Fund, Indianapolis, Indiana; Grants HL-06308 and HL-07182 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; Public Health Service Grant RR00750, General Clinical Research Center; The American Heart Association, Indiana Affiliate, Indiana; and by the Veterans Administration Medical Center, Indianapolis, Indiana. Manuscript received June 20, 1983; revised manuscript received September 26, 1983, accepted September 30, 1983.

Address for reprints: James J. Heger, MD, Associate Professor of Medicine, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46223.

0735-1097/84/$3.00

JACC Vol. 3, No. 3
March 1984:857–64



CIBENZOLINE

Figure 1. Molecular structure of cibenzoline.

Methods

Patients. The study group comprised 20 men and 6 women whose ages ranged from 29 to 73 years (mean 56 ± 11) who were being treated for a symptomatic ventricular arrhythmia (Table 1). Each patient had received 2 to 7 (mean 3.3 ± 1.3) trials of antiarrhythmic drugs that were either ineffective or produced intolerable side effects. Sixteen patients had coronary artery disease evidenced by a history of myocardial infarction or the presence of coronary artery disease by coronary arteriography. Four patients had congestive cardiomyopathy documented by absence of coronary artery disease and presence of a dilated hypokinetic left ventricle on two-dimensional echocardiography and cardiac catheterization. Two patients had mitral valve prolapse documented by echocardiogram and four patients had primary electrical disease defined as no evidence of heart disease by clinical examination, echocardiography and cardiac catheterization. One patient diagnosed as having primary electrical disease refused coronary catheterization but had no evidence of heart disease. Each patient gave informed consent for participation in the study protocol which was approved by the Committee for Protection of Human Subjects of Indiana University.

Treatment Protocol

At entry a complete history and physical examination were performed and all antiarrhythmic drugs were discontinued for at least 48 hours. The treatment protocol (Fig. 2) began with a 3 day initial control period during which all control data were obtained, followed by a treatment phase in which oral cibenzoline was administered at each dosage level for 2 day periods.

Table 1. Patient Population

Case	Age (yr) & Sex	Heart Disease	Clinical Arrhythmia†	Arrhythmia† on Maximal Cibenzoline Dose (plasma level ng/ml)
1	53M	CAD	VF	VT-NS
2	71M	CAD	VT-NS	PVC* (344)
3	58M	CAD	VT-NS	VT-NS (690)
4	56M	CAD	VF	VT-NS
5	52M	CAD	VT-NS	VT-S* (519)
6	29F	PED	PVC-sx	PVC* (577)
7	48M	MVP	VT-NS	VT-NS*
8	52M	CAD	VT-NS	PVC* (267)
9	68F	CAD	VT-S	VT-S (413)
10	68M	PED	PVC-sx	PVC*
11	47M	CAD	VF	VF
12	56M	PED	VF	VT-NS
13	52M	CAD	VT-NS	VT-NS
14	58M	CM	VT-NS	VT-NS
15	73F	CAD	VF	VT-NS
16	62M	CAD	VF	VT-NS
17	55M	CAD	VT-NS	VT-S
18	67M	CM	VF	VT-NS
19	40M	CAD	VT-NS	VT-NS
20	58F	CAD	VT-NS	VT-S
21	70M	PED	VT-S	VT-NS
22	48M	MVP	VT-S	VT-NS
23	58F	CAD	VT-NS	VT-NS
24	62M	CAD	VT-S	VT-S (385)
25	34F	PED	VT-NS	VT-NS
26	67M	CM	VT-S	VT-S

*Discharged receiving cibenzoline; †Arrhythmia found on telemetry, 24 hour continuous electrocardiogram or electrophysiologic study; CAD = coronary artery disease; CM = congestive cardiomyopathy; F = female; M = male; MVP = mitral valve prolapse; PED = primary electrical disease; PVC = asymptomatic premature ventricular complexes; PVC-sx = symptomatic premature ventricular complexes; VF = ventricular fibrillation; VT-NS = nonsustained ventricular tachycardia; VT-S = sustained ventricular tachycardia.

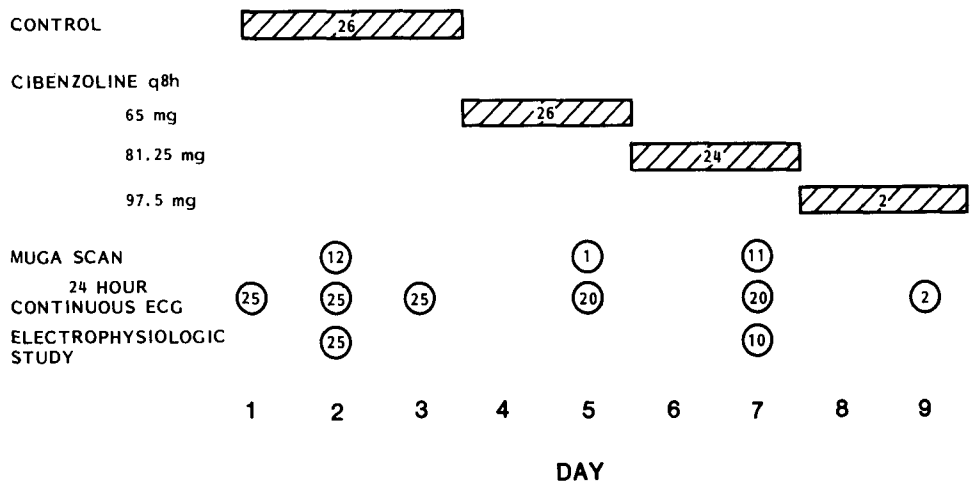


Figure 2. Patient protocol. The numbers inside the **rectangles** and **circles** represent the number of patients that underwent this portion of the protocol. ECG = electrocardiogram; MUGA scan = multigated technetium blood pool scan; q8h = every 8 hours.

Electrocardiographic monitoring. Arrhythmias were monitored continuously during the entire study using a computer-based telemetry system (Hewlett-Packard). The system indicated premature ventricular complex trends and episodes of ventricular tachycardia defined as three or more consecutive premature ventricular complexes. Each episode of ventricular tachycardia was reviewed and confirmed by an investigator. Daily scalar electrocardiograms at rest were performed on each patient for measurement of spontaneous cycle length and PR, QRS and QT intervals.

Three 24 hour continuous electrocardiographic recordings were performed during the control period and one recording was performed during the second day of each dosage level of cibenzoline. The recordings were analyzed (Cardio Data Corporation) to determine hourly premature ventricular complex frequency and the presence of ventricular tachycardia.

Continuous electrocardiographic recording was performed using a two channel Avionics recorder (model 445B) with computerized quantitation of premature ventricular complexes using a template system (3). Reproducibility and accuracy of premature ventricular complex quantitation have been shown to be within 2%. Premature ventricular complex frequency was expressed as the mean premature complexes/h for a 24 hour period. For recordings lasting less than 24 hours, the data were analyzed by determining the mean premature ventricular complexes/h for the hours monitored. All episodes of ventricular tachycardia were recorded on hard copy and were confirmed by the primary investigator.

In comparing premature ventricular complex frequency between 24 hour electrocardiographic recordings a change in premature ventricular complex frequency of 83% or greater was judged to be significant as derived from the analysis by Morganroth et al. (4). Because these authors employed a two-tailed t statistic to determine the range of spontaneous variability of premature ventricular complex frequency, it follows that both an increase and a decrease of 83% or more represent a significant change in arrhythmia frequency. The criteria of Velebit et al. (5) were also employed to determine drug-induced aggravation of arrhythmia.

Multigated blood pool scans with technetium-labeled red blood cells were performed in 12 patients during control and at the maximal dose of cibenzoline for determination of left ventricular ejection fraction.

Electrophysiologic studies. Electrophysiologic study was performed in 25 of 26 patients during control state and repeated in 10 patients while they received the maximal dose of cibenzoline. For each study, patients were in the postabsorptive, nonsedated state. Before the control electrophysiologic study, all cardioactive medications were discontinued for a period exceeding 5 elimination half-lives of the respective medications. During cibenzoline treatment, the electrophysiologic study was repeated after patients received at least 48 hours of maximal cibenzoline dosage. Two or three multipolar electrode catheters were inserted percutaneously and advanced to the heart under fluoroscopic guidance. The catheters were positioned in the high lateral right atrium, across the tricuspid valve in the region of the His bundle and in the right ventricle.

Intracardiac electrograms and standard electrocardiographic leads I, II, III and V_1 were displayed simultaneously on a multichannel oscilloscope (Electronics for Medicine) and recorded at paper speeds of 75 to 150 mm/s. Intracardiac and surface electrograms were recorded at frequencies of 30 to 500 and 0.1 to 20 Hz, respectively.

Pacing protocol. Pacing was performed using a programmable stimulator (MECA) that delivered square wave stimuli of 2.0 ms duration at two times late diastolic threshold. The following pacing protocol was used in an attempt to initiate ventricular tachycardia:

1) *High right atrial pacing* was performed at progressively faster rates until atrioventricular (AV) block occurred.

2) *Premature right atrial stimulation* was performed at two or more pacing cycle lengths. Premature stimuli were introduced beginning late in diastole and at 10 to 20 ms decrements until atrial refractoriness was obtained.

3) *Premature right ventricular stimulation* was performed during sinus rhythm and ventricular pacing at cycle lengths of 600, 500 and 400 ms. Premature stimuli (S_2) were initiated after every eighth paced or sinus complex beginning in late diastole and the coupling interval was progressively shortened until ventricular refractoriness was reached. If ventricular tachycardia was not reproducibly initiated, the shortest coupling interval (S_1S_2) resulting in consistent ventricular capture was chosen. A second premature stimulus (S_3) was then introduced beginning at an S_2S_3 interval, which was 100 ms longer than the S_1S_2 interval. The S_2S_3 interval was shortened by 10 to 20 ms decrements until S_3 no longer resulted in ventricular depolarization. If ventricular tachycardia was not reproducibly induced, the S_1S_2 interval was increased by 50 ms and the S_2S_3 interval was set at 100 ms longer than the S_1S_2 interval. The S_2S_3 interval was shortened until the ventricle was refractory to S_3, at which time the S_1S_2 interval was decreased by 10 ms until S_3 again resulted in ventricular depolarization. This pacing sequence was repeated until the ventricle was refractory to S_2.

4) *Three to eight complexes of right ventricular burst pacing* were initiated at a cycle length of 250 ms or more.

5) *If ventricular tachycardia was not induced at the first site tested,* a second right ventricular pacing site was chosen and programmed ventricular stimulation was repeated.

6) *In one patient, three ventricular extrastimuli were used* ($S_2S_3S_4$) to induce ventricular tachycardia while pacing the right ventricular apex.

Laboratory tests. These were performed to evaluate hepatic, renal and hematologic function during the control period and at each dose level. Trough plasma cibenzoline concentrations were determined in seven patients during maximal cibenzoline dosage and at end of each dosage schedule.

Follow-up. Patients who were discharged receiving cibenzoline were followed up in an outpatient antiarrhythmic drug clinic 1 month after discharge and every 3 months thereafter. Interim history, physical examination, electrocardiogram at rest, laboratory tests of hepatic, renal and hematologic function and a 24 hour continuous electrocardiogram were performed at each visit.

Statistical methods. Appropriate unpaired or paired Student's *t* testing was performed on the data to evaluate the statistical significance (6). Statistical significance was assigned to a probability (p) value less than 0.05.

Results

Overall outcome. Figure 3 diagrams the outcome of 26 patients who entered the study. The maximal dosage of cibenzoline was 65 mg in 2 patients, 81.25 mg in 22 patients and 97.5 mg in 2 patients. The dose was limited to 65 mg in two patients because of a significant increase (>83%) in premature ventricular complex frequency and in two other patients the dose was increased to 97.5 mg because premature ventricular complex frequency was decreased at lower dosage, but ventricular tachycardia was not completely suppressed. In both of the latter patients, the higher dose failed to prevent spontaneous ventricular tachycardia and one of these patients had the new appearance of sustained ventricular tachycardia that was thought to be drug related.

Cibenzoline was discontinued in 15 patients because it failed to prevent spontaneous episodes of ventricular tachycardia at the highest tested dose, in 4 patients because cibenzoline failed to prevent ventricular tachycardia induc-

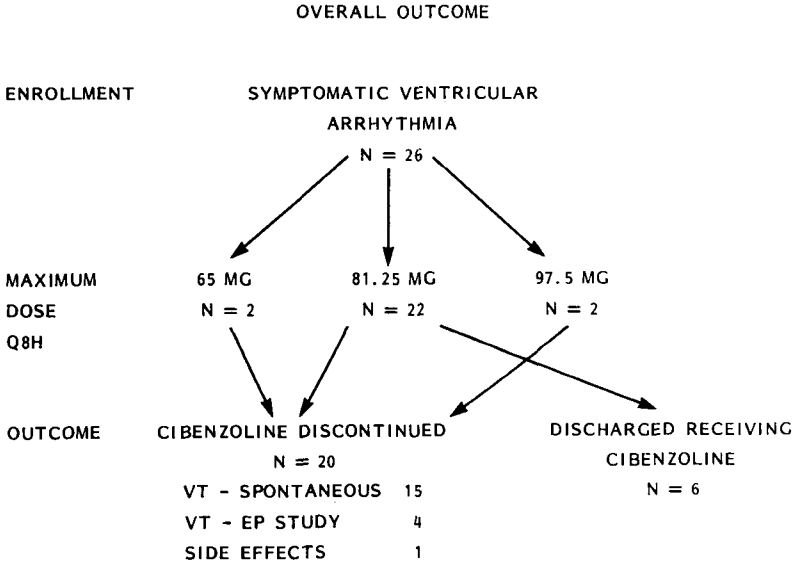


Figure 3. Overall outcome for the 26 patients enrolled in the study of cibenzoline. EP = electrophysiologic study; N = number of patients; Q8H = every 8 hours; VT = ventricular tachycardia.

Table 2. Scalar Electrocardiographic Data (ms)

Intervals	(n)	Control	Cibenzoline 65 mg	Cibenzoline 81.25 mg	p Value*
PR	(21)	170 ± 21	180 ± 26	193 ± 27	< 0.001
QRS	(22)	100 ± 28	108 ± 32	117 ± 33	< 0.001
RR	(22)	806 ± 116	791 ± 137	760 ± 97	< 0.02
QT	(22)	395 ± 43	399 ± 39	404 ± 32	NS
QT_c†	(22)	443 ± 47	455 ± 61	467 ± 47	< 0.05

*Student's paired *t* test comparing 81.25 mg dose with control. †Corrected by Bazett's formula ($QT_c = QT/\sqrt{RR}$).

tion at electrophysiologic study and in 1 patient because of intolerable side effects. In six patients, cibenzoline was continued for outpatient antiarrhythmic drug therapy at a dose of 81.25 mg every 8 hours. Cibenzoline was judged effective in these six patients because it prevented spontaneous nonsustained ventricular tachycardia in six and ventricular tachycardia induction during electrophysiologic study in three. One of the six patients did not undergo electrophysiologic testing.

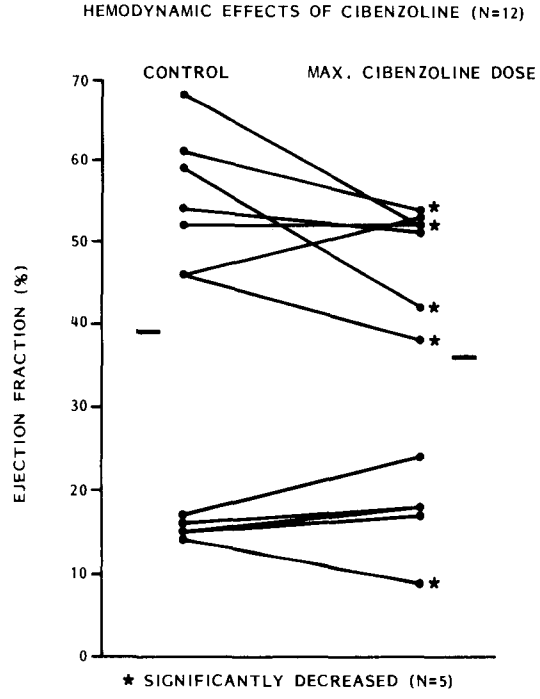
Scalar electrocardiographic data. The dose-related effects of cibenzoline on electrocardiographic intervals are lited in Table 2. PR interval could not be measured in one patient who had atrial fibrillation. PR, QRS, RR and corrected QT interval by Bazett's formula increased slightly but insignificantly during cibenzoline therapy in a dose-related fashion.

Left ventricular function. No patient had worsening or new onset of clinical signs or symptoms of congestive heart failure during therapy with cibenzoline. There was no significant change in mean ejection fraction during the control period (0.39 ± 0.21) compared with that at the maximal cibenzoline dosage (0.36 ± 0.17) in the 12 patients who had multigated blood pool scans at control and during maximal cibenzoline dosage (Fig. 4). However, ejection fraction decreased by 5% or greater in five patients, increased by 5% or less in two patients and did not change in the remaining five patients. The heart rate at maximal cibenzoline dose was within 10% of the control rate in 7 of the 12 patients. In the other five patients heart rate at rest increased during cibenzoline therapy (mean 33 ± 16%, range 13 to 48) and three of these five patients had a significant decrease in left ventricular ejection fraction.

Continuous electrocardiographic recording. During the protocol, 22 patients had data from 24 hour continuous electrocardiographic recordings performed at control and during maximal cibenzoline dosage. Loss of the recording data due to technical problems occurred in two patients and cibenzoline therapy was terminated in two patients before a recording could be obtained. The 72 hour control period recordings disclosed that 16 patients had ventricular tachycardia and six patients had no ventricular tachycardia. Of the 16 patients who had ventricular tachycardia during control, 8 patients continued to have ventricular tachycardia at maximal tolerated cibenzoline dosage while no ventricular tachycardia was present in the other 8 patients. Of the six patients who had no ventricular tachycardia during control study, ventricular tachycardia was recorded in three patients during maximal cibenzoline dosage and three patients continued to have no ventricular tachycardia.

The effect of cibenzoline on hourly premature ventricular complex frequency (Fig. 5). Overall, mean hourly premature ventricular complex frequency did not significantly change (mean 507 ± 521 to 350 ± 515 premature ventricular complexes/h), but in 7 of 22 patients mean hourly premature ventricular complex frequency decreased more than 83% at maximal cibenzoline dosage compared with the control period. Three patients exhibited a significant increase in pre-

Figure 4. Hemodynamic effects measured by multigated technetium blood pool scanning (MUGA) for each patient before (**left**) and during (**right**) cibenzoline therapy. There was no significant change in the mean ejection fraction for the group of 12 patients as represented by the **solid bars.** The asterisk (*) refers to a significant decrease, that is, 5% or more in ejection fraction during cibenzoline therapy compared with control. MAX. = maximal.



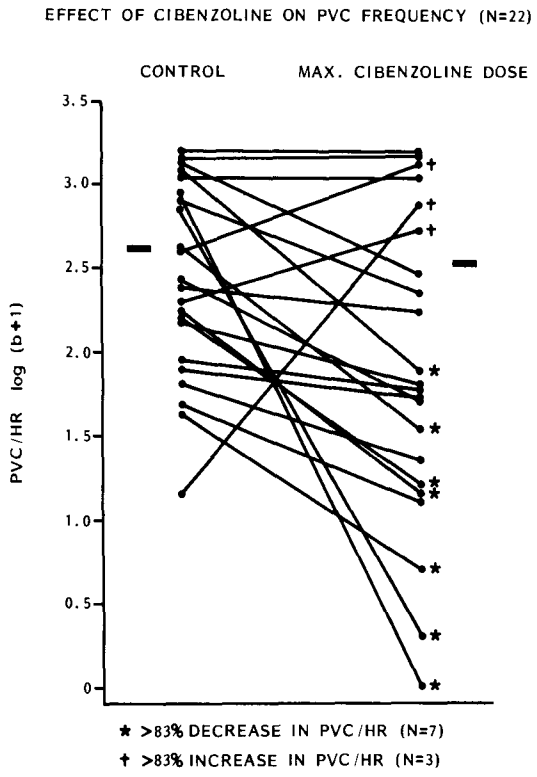


Figure 5. Effect of cibenzoline to reduce premature ventricular complexes (PVC) is shown during the control period (**left**) and during cibenzoline therapy (**right**) for the 22 patients who had continuous electrocardiographic recording. There was no significant change in the number of premature complexes per hour for the overall study group (n = 22) as represented by the **solid bars**. The **ordinate** represents the average hourly number of these complexes over 72 hours during the control period and over 24 hours during maximal cibenzoline therapy for each patient. The **asterisks** (*) denote the seven patients with a greater than 83% decrease in premature ventricular complexes per hour and the **crosses** (+) denote the three patients with a greater than 83% increase in such complexes per hour.

mature ventricular complex frequency defined as premature ventricular complex increase of greater than 83% compared with control values. One of the three patients had a 3-fold increase in premature ventricular complex frequency and developed spontaneous sustained ventricular tachycardia, one patient had a 40-fold increase and one patient exhibited a 4-fold increase in premature ventricular complex frequency.

Electrophysiologic effects. Twenty-five patients had an electrophysiologic study during the control period and one patient refused study. During maximal cibenzoline therapy 10 patients had a repeat electrophysiologic study, while repeat electrophysiologic studies were not performed in the other 15 patients because ventricular arrhythmias were judged to have not improved or worsened in 14 patients and cibenzoline had been discontinued in 1 patient because of side effects.

Table 3 summarizes the data from clinical electrophysiologic studies for the 10 patients who underwent electrophysiologic study at control and maximal cibenzoline dosage. Of note, ventricular effective and functional refractory periods prolonged significantly. In the patients who had ventricular tachycardia induced at both studies, the ventricular tachycardia cycle length prolonged significantly during cibenzoline therapy.

Table 3. Electrophysiologic Effects (in ms) of Cibenzoline in 10 Patients

	Control	Cibenzoline	p Value†
Sinus cycle length	774 ± 188	690 ± 125	NS
AH interval	80 ± 22	88 ± 18	NS
HV interval	53 ± 14	60 ± 11	< 0.07
Atrium			
ERP	243 ± 28	239 ± 33	NS
FRP	276 ± 42	279 ± 33	NS
AV node			
Max 1:1 CL	345 ± 70	348 ± 52	NS
ERP	285 ± 65	284 ± 35	NS
FRP	390 ± 56	389 ± 45	NS
RV apex			
ERP	223 ± 16	241 ± 22	< 0.001
FRP	247 ± 18	264 ± 25	< 0.02
VT CL (n = 7)*	210 ± 31	260 ± 46	< 0.05

*Two patients had no inducible ventricular tachycardia while receiving cibenzoline. One patient had no inducible ventricular tachycardia at control study or while receiving cibenzoline. †Student's paired *t* test. AV = atrioventricular; CL = cycle length; ERP = effective refractory period; FRP = functional refractory period; Max 1:1 CL = the fastest rate at which high right atrium could be paced and 1:1 AV conduction could be maintained; RV = right ventricular; VT = ventricular tachycardia.

Nine of the 10 patients had ventricular tachycardia induced during the control electrophysiologic study. During maximal cibenzoline therapy, ventricular tachycardia was still induced in seven of the patients while cibenzoline prevented induction of tachycardia in two patients. One patient had no arrhythmia induced at control electrophysiologic study or while receiving cibenzoline. Induction of ventricular tachycardia was accomplished with two premature stimuli during right ventricular apical pacing in all nine patients at control electrophysiologic study. Of the seven patients who had ventricular tachycardia induced during maximal cibenzoline therapy, five patients required two premature stimuli during right ventricular apical pacing, one patient had ventricular tachycardia induced with atrial pacing and one patient required three premature extrastimuli from the right ventricular apex to induce ventricular tachycardia. Therefore, ventricular tachycardia was more easily induced in one patient, more difficult to induce in one patient and could not be induced in two patients.

Side effects. Four patients had side effects that required discontinuation of cibenzoline. In two patients, a significant increase in premature ventricular complex frequency was accompanied by worsened symptoms of palpitation, and one patient developed sustained ventricular tachycardia that re-

quired multiple cardioversions and disappeared only after 8 hours had elapsed from the last cibenzoline dose. One patient had nausea and abdominal pain and refused to continue taking the drug. Of note, this patient had similar symptoms with procainamide and quinidine. Two other patients experienced mild anticholinergic effects that consisted of blurred vision and dry mouth, which did not require a change in therapy. No patient exhibited any deterioration of hepatic, renal or hematologic function. Plasma cibenzoline levels ranged from 200 to 700 ng/ml in the seven patients who had levels measured during maximal cibenzoline therapy (Table 1).

Follow-up. Six patients were discharged receiving cibenzoline and three of them have continued cibenzoline treatment during a mean follow-up period of 10 ± 4 months (range 3 to 17). Of the six patients who were discharged receiving cibenzoline, one patient was treated initially for symptomatic premature ventricular complexes and five patients were treated for recurrent symptomatic nonsustained ventricular tachycardia. The patient referred for symptomatic premature ventricular complexes had complete suppression of three premature complexes on 24 hour continuous electrocardiographic recording at maximal cibenzoline dose and has remained symptom-free during the follow-up period. Of the five patients treated for symptomatic nonsustained ventricular tachycardia, two have remained symptom-free, one died of cardiogenic shock occurring after an acute myocardial infarction and two (both with ventricular tachycardia during electrophysiologic study while receiving cibenzoline) have continued to experience palpitation and had nonsustained ventricular tachycardia recorded on continuous electrocardiographic monitoring. Both of these patients have stopped taking cibenzoline.

Discussion

Clinical efficacy. Patients enrolled in the protocol can be separated into two groups. Twelve patients (Group I) had a history of sustained ventricular tachycardia or ventricular fibrillation requiring cardioversion or defibrillation and 14 patients (Group II) had a history of either symptomatic nonsustained ventricular tachycardia or frequent premature ventricular complexes. No patient in Group I had an adequate antiarrhythmic response to cibenzoline, although 3 of the 12 patients did exhibit complete suppression of spontaneous ventricular tachycardia during telemetry and continuous electrocardiographic recording. Two of these three patients had sustained and one had nonsustained ventricular tachycardia during electrophysiologic study while receiving maximal cibenzoline therapy. In contrast, 4 of 14 patients in Group II were considered to have an adequate antiarrhythmic response to cibenzoline and 7 (50%) of 14 exhibited no spontaneous ventricular tachycardia during telemetry and continuous electrocardiographic recording.

The study group included only patients who had been refractory to between two and seven other antiarrhythmic drugs. The efficacy of any antiarrhythmic drug in this study group would be expected to be limited. Because of this, the value of cibenzoline in treating patients who have ventricular arrhythmias that have not been refractory to other antiarrhythmic agents may be equal to or superior to that of antiarrhythmic drugs currently available for clinical use.

Criteria and predictors of efficacy. Only 4 (15%) of the 26 patients enrolled in the protocol met two criteria of antiarrhythmic efficacy, that is, suppression of spontaneous ventricular tachycardia recorded by telemetry and continuous electrocardiographic recording and prevention of ventricular tachycardia induction at electrophysiologic study during maximal cibenzoline therapy. If suppression of spontaneous ventricular tachycardia was the only criterion employed to determine successful therapy, then 7 (27%) of 26 patients would have been considered to have an adequate antiarrhythmic regimen. Of these seven patients, two had no ventricular tachycardia induced at electrophysiologic study, were discharged receiving cibenzoline and have remained asymptomatic during long-term therapy. In another two of these seven patients, cibenzoline prevented spontaneous ventricular tachycardia during continuous electrocardiographic recording and telemetry, but ventricular tachycardia was induced at electrophysiologic study during maximal cibenzoline therapy. Both patients had symptomatic, nonsustained ventricular tachycardia during follow-up and cibenzoline was discontinued. One other patient did not have electrophysiologic testing and has continued cibenzoline long term. In the remaining two patients, cibenzoline was discontinued after rapid sustained ventricular tachycardia was induced during electrophysiologic study. Although the number of patients in the present study is small, it appears that noninducibility during electrophysiologic study coupled with no spontaneous ventricular tachycardia best predicted the long-term efficacy of cibenzoline therapy.

Continuous electrocardiographic recording. In this study we found that cibenzoline treatment decreased premature ventricular complex frequency by greater than 83% in 7 of 22 patients. Only two of the seven patients were from Group I, that is, patients who had sustained ventricular tachycardia or ventricular fibrillation, while five patients were from Group II. Therefore, using suppression of premature ventricular complexes as an indicator of antiarrhythmic effect, cibenzoline seemed to be more effective in patients with symptomatic frequent premature ventricular complexes or nonsustained ventricular tachycardia as compared with patients who had sustained ventricular tachycardia or ventricular fibrillation.

Suppression of premature ventricular complexes versus ventricular tachycardia. For procainamide it has been reported that the plasma concentration needed to suppress ventricular tachycardia was lower than that needed to reduce

significantly the premature ventricular complex frequency (7). We examined this hypothesis in our 22 patients and found that in 12 patients cibenzoline did not suppress ventricular tachycardia or significantly reduce premature ventricular complex frequency, while in 5 patients cibenzoline suppressed spontaneous ventricular tachycardia and significantly reduced premature ventricular complex frequency. In three patients, cibenzoline suppressed ventricular tachycardia but did not significantly decrease premature ventricular complex frequency. Of note, in the other two patients cibenzoline significantly suppressed premature ventricular complex frequency (93% and 92%, respectively) but spontaneous ventricular tachycardia was still present. Therefore, it appears that in some patients a given plasma cibenzoline concentration produced significant suppression of premature ventricular complexes without suppressing ventricular tachycardia and that significant suppression of premature ventricular complexes alone does not accurately predict suppression of ventricular tachycardia.

Hemodynamics. Although the mean left ventricular ejection fraction did not change in our study patients, there was a significant decrease in ejection fraction during cibenzoline therapy in 5 of 12 patients. In contrast with reports on the hemodynamic effects of disopyramide (8), there is much less depression of cardiac function produced by cibenzoline. No patient with a control ejection fraction less than 40% had a decrease during cibenzoline treatment and no patient developed clinical heart failure while receiving cibenzoline.

Clinical electrophysiologic and electrocardiographic data. There was a dosage-related increase in PR, QRS and QT intervals. None of the changes were marked and no patient developed heart block or an intraventricular conduction defect. In spite of significant prolongation of the PR interval during cibenzoline therapy, neither AH nor HV interval prolongation reached statistical significance. Prolongation of the PR interval reached significance because of modest prolongation of the PA, AH and HV intervals.

Cibenzoline decreased spontaneous sinus cycle length, which may reflect the vagolytic properties of the drug. There was a modest prolongation of the right ventricular effective (18 ± 22 ms) and functional (17 ± 25 ms) refractory periods and an increase in cycle length of induced ventricular tachycardia (50 ± 46 ms).

We evaluated the data obtained from the control electrophysiologic study and found that no measured variable or group of variables was predictive of antiarrhythmic drug efficacy. Inability to induce ventricular tachycardia during electrophysiologic study in patients receiving maximal cibenzoline therapy appeared to be an indicator of a favorable long-term response.

Conclusion. Cibenzoline is a well-tolerated antiarrhythmic agent that effectively suppresses symptomatic ventricular arrhythmias in some patients not successfully treated with conventional antiarrhythmic drugs. In the patients in this study, cibenzoline appeared to be reasonably effective in those patients with symptomatic premature ventricular complexes or nonsustained ventricular tachycardia but ineffective in the patients with sustained ventricular tachycardia or ventricular fibrillation.

We acknowledge Hoffmann-LaRoche Corporation for their analysis of serum cibenzoline concentrations, Linda Richmond for her technical assistance in data collection and Jill Cottengim for her help in preparation of the manuscript.

References

1. Miller JS, Vaughn William ES. Effects on rabbit nodal, atrial, ventricular, and Purkinje cell potentials of a new antiarrhythmic drug, cibenzoline, which protects against action potential shortening in hypoxia. Br J Pharmacol 1982;75:469–78.
2. Investigational Drug Brochure: Cibenzoline. New Jersey: Hoffmann-LaRoche, 1982.
3. Hubelbank M, Feldman CL. A 60X computer-based Holter tape processing system. Med Instrum 1978;12:110–3.
4. Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB. Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 1978;58:408–14.
5. Velebit V, Podrid P, Lown B, Cohen B, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982;65:886–94.
6. Snedecor GW, Cochran WG. Statistical Methods. 6th ed. Ames, Iowa: Iowa State University Press, 1967.
7. Myerberg RJ, Kessler KM, Kiem I, et al. Relationship between plasma levels of procainamide, suppression of premature ventricular complexes and prevention of recurrent ventricular tachycardia. Circulation 1981;64:280–90.
8. Jensen G, Sigurd B, Uhrenbolt A. Hemodynamic effects of intravenous disopyramide in heart failure. Eur J Clin Pharmacol 1975;8:167–78.